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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/309,038	05/10/99	HEIFETZ	P	A-30496B

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EXAMINER	
MEHTA, A	

ART UNIT	PAPER NUMBER
1638	14

DATE MAILED: 10/11/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/309,038	HEIFETZ ET AL.	
	Examiner	Art Unit	
	Ashwin Mehta	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40,46-52,56-65,70 and 73-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40,46-52,56-65,70 and 73-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. The objection to the specification is withdrawn in light of Applicant's amendment.

3. The objection to claims 45, 52-55, and 59-61 is withdrawn in light of the cancellation of claims 45 and 53-55.

4. The rejections of claims 1-40, 45-70, and 72 under 35 U.S.C. 112, second paragraph, in items 3-5 of the last office action are withdrawn in light of the claim amendments.

5. The rejections of claims 1, 10, 11, 45, 46, 52, 63, 65, and 66 under 35 U.S.C. 102(a) or (b) in items 9 and 10 of the last office action are withdrawn in light of the claim amendments.

Claim Objections

6. Claims 2 and 13 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 2 and 13 attempt to limit their parent claims by requiring the cells of the method of the parent claims to be virus resistant or tolerant. However, the amended parent claims indicate that the cells produced by their methods are virus resistant or tolerant.

7. Claim 64 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim attempts to limit parent claim 63 by requiring the expression of the viral genome or portion thereof to be reduced. However, the components that can make up the DNA construct of claim 63 will not change whether or not the expression is reduced.

Claim Rejections - 35 USC § 112

8. Claims 56-58, 60, and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because they are dependent on cancelled claim 55.

9. Claims 63-64 (both amended) 65, 69 (amended), and 70, remain, and claims 1(amended), 2-10, 11-12 (both amended), 13-22, 23 (amended), 24-40, 46 (amended), 47, 48 (amended), 49-52, 56-62 are, and new claims 74-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record stated in the last office action on pages 4-6 under item 6 for claims 63-70 and 72.

Applicants traverse the rejection in the paper submitted 23 July 2001. Applicants argue that the viral genome or portions thereof of the present invention are described on page 17, line 27 to page 18, line 13 of the specification. Applicants argue the dsDNA, dsRNA, plus and minus strand ssRNA, antisense RNA viruses and retroviruses are controlled with the invention (response, paragraph bridging pages 5-6).

Applicant's arguments have been fully considered as they apply to claims 1-40, 46-52, 56-65, 69, 70, and new claims 74-75, but were not found persuasive. The portion of the specification cited by the Applicants just reiterates Applicant's remarks. The numerous DNA sequences of all the viral genomes or portions thereof encompassed by the claims are not described. The DNA sequences described on pages 26-43 of the specification do not provide any information regarding the sequences and functions of all the sequences encompassed by the claims. The specification also does not provide describe the portions of viral genomes, which encompass non-coding sequences, that are functional with the claimed invention. See Fiers vs. Sugarno, cited in the last in office action.

10. Claims 1 (amended), 2-10, 11-12 (both amended), 13-22, 23 (amended), 24-40, 46 (amended), 47-52, 56-61, 62-64 (all amended), 65, 69 (amended), 70 remain and new claims 73-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains,

or with which it is most nearly connected, to make and/or use the invention, for the reasons of record stated in the last office action on pages 6-7 under item 7 for claims 1-40, 45-70, and 72.

Applicants traverse the rejection in the paper filed 23 July 2001. Applicants argue that mere unpredictability of the result of the experiment is not a consideration (response, page 7). Applicants submit a declaration signed by one of the inventors, Dr. Jan Gielen, which present data indicating that transgenic plants transformed with the constructs of Example 9 of the specification displayed resistance to rhizomania (a disease caused by the furovirus, beet necrotic yellow vein virus). This declaration addresses enablement of the invention for use in plant cells with furoviruses, and when the DNA or RNA fragments comprises the entire coding sequence of a viral gene.

However, the declaration does not address the enablement of the invention for use with all virus genomes, or any portion of a viral genome, nor non-plant cells and non-plant viruses. Neither the declaration nor the specification provides any teaching indicating why the claimed method would work against all viruses and in all cell types. For example, Voinnet et al. teach that numerous viruses encode viral suppressors of post-transcriptional gene silencing, which acts by directing RNA degradation, and allow viruses to infect host plants (page 14147, 14151-14152). Therefore the claimed invention would not reduce the expression of viral genomes that have evolved such suppressors.

Montgomery et al. (Trends Gen., July 1998, Vol. 14, pages 255-258) discuss the effect of double-stranded RNA as a mediator in sequence-specific genetic silencing, and question whether such RNA-interference mechanisms have applications outside of plants and nematodes. The authors note that mammalian cells exhibit a global antiviral response to double-stranded RNA in

which the PKR protein kinase recognizes dsRNA and initiates a non-specific response that results in general translation arrest, and only if the dsRNA is produced extracellularly (page 258). The claimed methods call for introducing the claimed nucleic acid constructs into cells. A general translation arrest also raises the question of whether the claimed invention would produce viable mammalian cells. Montgomery et al. also teach that the precise nature of interfering RNA, single- versus double-stranded material, has yet to be characterized in vertebrate and other systems (page 258). Further, regarding claims 31-33, the specification does not teach how the sense-and antisense-RNA fragments would still be on the same expressed RNA molecule when it also has to include functional genes, or regulatory sequences initiate or terminate transcription. Further regarding claims 56-58: the specification does not teach inheritance of viral resistance in progeny of plants in which RNA was introduced. It is not clear how the progeny would be have increased virus resistance since the RNA fragments would not be inherited. Given the breadth of the claims encompassing a method to reduce viral genome expression in all cell types, of all viruses, and with any portion of any viral genome, the unpredictability of the art, and lack of guidance of the specification as discussed above and in the previous office action, undue experimentation would be required to practice the claimed invention. It is suggested that the claims be amended to only encompass plant cells and gene coding sequences from furoviruses.

11. Claim 70 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention, for the reasons of record stated in the last office action on pages 7-9 under item 8 for claims 1-40, 45-70, and 72.

Applicants amended claims 1, 12, 46, and 64 in the response submitted 23 July 2001, overcoming the rejection for claims 1-40, 45-69, and 72. However, claim 70 is still drawn to alteration of the target gene.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-30, 33-40, 46-52, 56-65, 70, and 73-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sijen et al in view of Fire et al, Applicant's admitted state of the prior art, and Keddie et al.

The claims are broadly drawn towards a method for conferring resistance or tolerance to any virus upon any cell comprising introducing into a cell a sense RNA fragment of a viral genome or portion thereof and an antisense RNA fragment of said viral genome or portion thereof, wherein said fragments form a double-stranded molecule and wherein expression of said viral genome or portion thereof in said cell is reduced; or wherein the cell is a plant cell; or wherein the RNA fragments are in two different molecules, or mixed before introduction into the cell, or introduced sequentially into the cell, or are comprised in the same RNA molecule; or said

method wherein the RNA fragments are expressed from DNA; a cell obtained from said method; a plant obtained from said cell; seed derived from said plant; any DNA fragment comprising a first DNA sequence capable of expressing in any cell sense and anti-sense RNA fragments of a target gene, operably linked to a bi-directional promoter; or a DNA construct comprising a first DNA sequence capable of expressing in a cell sense- and anti-sense RNA fragments of a viral genome or portion thereof.

Sijen et al. teach RNA-mediated virus resistance in transgenic plants comprising transforming plant cells with a DNA construct comprising the a defective cowpea mosaic virus movement protein gene operably linked to the CaMV 35 S promoter; transformed plants were found to be resistant to CPMV RNA; Resistance was directed against the replication of the viral segment from which the transgene was derived. When sequences corresponding to the to the full-length MP transgene were inserted into the RNA of the potexvirus, potato virus X, and injected into the plant, the plant remained free of PVX-specific symptoms. Their experiments led the authors to conclude that heterologous RNA molecules can become a victim of silencing if it harbors sequences homologous to the transcribed region of a transgene that is post-transcriptionally silenced. Sijen et al propose that the resistance mechanism may involve formation and subsequent degradation of double-stranded RNA produced from the expressed viral sequences (pages 2277-2280; 2288-2289).

Sijen et al do not teach DNA constructs expressing both sense and anti-sense RNA fragments of a viral genome or portion thereof, or a method to reduce viral genome expression comprising introducing into a cell sense and antisense RNA fragments of a viral genome, or tissue-specific, developmentally regulated, inducible, or bi-directional promoters.

Fire et al. teach genetic interference in nematodes conferred by introduction of sense and anti-sense strands of a target gene, unc-22; interference was seen both when the strands were mixed before inoculation, and when they were not mixed prior to inoculation; Fire et al. assert that such interference might also operate in plants (pages 808-810).

Keddie et al. teach a bi-directional promoter (pages 332-338). This reference is cited to address the limitation of bi-directional promoters.

Applicant's specification admits that the prior art teaches plant tissue specific, developmentally regulated and inducible promoters, and use of intron sequences (pages 20-22).

It would have been obvious and within the scope of one of ordinary skill in the art to modify the method of conferring plant virus-resistance of Sijen et al. by stably transforming a plant cell with a DNA construct that comprises DNA sequences encoding sense and antisense RNA fragments of the CPMV MP gene, operably linked to promoters such that sense- and anti-sense RNA fragments get expressed and form a dsRNA molecule, following the demonstration by Fire et al. that injecting double-stranded RNA of the unc-22 gene into nematodes reduces unc-22 expression. As speculated by Sijen et al., and demonstrated by Fire et al., it is the formation of the dsRNA that is important for the silencing effect. Therefore it is obvious that there can be many variations in the manner in which the sense- and antisense-encoding DNA sequences can be arranged in the DNA construct and expressed, which amount to an optimization of process parameters. That is, it is obvious that the two sequences can be on the same strand of DNA of the DNA construct, or on complementary strands, or on different DNA constructs that get co-transformed into the cell, and still form two complementary RNA molecules. The sense- and anti-sense-encoding DNA sequences can be operably linked to any of a variety of different

constitutive, developmentally regulated, inducible, or tissue specific promoters known in the art, as admitted by Applicant's specification, or the bi-directional promoter taught by Keddie et al. Whether the two promoters regulating the two sequences are of the same type or different is a matter of choice. The sense-and anti-sense encoding DNA sequences can also be operably linked to the same promoter, forming a single RNA molecule, in which case a linker sequence obviously would be placed in between the two sequences so that steric hindrance would not prevent the expressed RNA from forming a double-stranded molecule. The linker sequence could also include a further regulatory sequence, such as the intron taught by Applicant's admitted state of the prior art. It would also have been obvious to collect seed from the transgenic plants for the purpose of propagation to produce progeny with the increased viral resistance. The sense- and anti-sense RNA fragments themselves could also be introduced into cells of a plant, as Fire et al. demonstrate that introduction of sense- and anti-sense fragments corresponding to the unc-22 target gene caused its silencing. As Fire et al. demonstrates, the sense-and anti-sense RNA fragments can be mixed prior to inoculation, or rapidly introduced sequentially. Many obvious variations on this theme would also have worked, as long as the sense- and anti-sense RNA sequences of the target gene are present so that they form a dsRNA molecule. That is, the sense- and anti-sense RNA sequences could also have been on the same molecule, since the important aspect is dsRNA formation. One would be motivated to prevent viral replication in cells by introducing sense and anti-sense RNA fragments that are from the virus's genome, given the teachings by Sijen et al. that RNA molecules that are homologous can be subjected to gene silencing, their suggestion that formation of double-stranded RNA molecules is part of the silencing process, and the demonstration by Fire et al. of silencing of a

gene by introduction of RNA molecules that represent sense-and anti-sense RNA fragments of that gene's mRNA, such that a dsRNA molecule is formed. One would also have been motivated by the assertion of Fire et al. that the mechanism may also operate in plants.

Summary

13. Claim 31 and 32 are deemed free of the prior art, given the failure of the prior art to teach or fairly a method for conferring virus resistance or tolerance to a cell comprising introducing into a cell a DNA molecule comprising first and second DNA sequences encoding sense and anti-sense RNA fragments of a viral genome or portion thereof, wherein the first and second DNA sequences are on the same DNA strand, said sense and anti-sense RNA fragments are on one RNA molecule, wherein the DNA molecule further comprises a linker between the two DNA sequences, wherein the linker comprises a functional gene. The prior art does not teach expression of an RNA molecule that has sense and corresponding anti-sense fragments that interact to form a double-strand region, while also having the transcript for a functional gene in between them.

14. No claim is allowed.

Contact Information

Any inquiry concerning this or earlier communications from the examiner should be directed to Ashwin Mehta whose telephone number is 703-306-4540. The examiner can normally be reached on 8:00 A.M to 5:30 P.M.. If attempts to reach the examiner by telephone

are unsuccessful, the examiner's supervisor, Paula Hutzell can be reached on 703-308-4310. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

A.M.
October 9, 2001

AMY J. NELSON, PH.D
PRIMARY EXAMINER